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Clinical and microbiological characteristics of Nocardiosis including those caused by emerging *Nocardia* species in Taiwan, 1998–2008

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Abstract

The genus of *Nocardia* is rapidly expanding and the species distribution varies with different geographical locations. We retrospectively reviewed the laboratory records of the bacteriology laboratory at National Taiwan University Hospital from January 1998 to June 2008 to identify patients with nocardiosis. During the study period, 164 isolates of *Nocardia* spp. were identified from 134 patients but only 113 patients had *Nocardia* infection. *Nocardia brasiliensis* (*n* = 54) was the most common pathogen, followed by *N. asteroides* (*n* = 36), *N. farcinica* (*n* = 7), *N. flavorosea* (*n* = 4), *N. otitidiscaviarum* (*n* = 3), *N. nova* (*n* = 3), *N. beijingensis* (*n* = 2) and one each of *N. puris*, *N. jinanensis* and *N. takedensis*. The major types of infection were cutaneous infection (56.6%), pulmonary infection (33.6%) and disseminated infection (7.1%). Eighty-eight patients received sulfonamide-containing antibiotic and eight of 100 patients with available data on outcomes died during the episode of nocardiosis. In conclusion, the clinical and microbiological manifestations of Nocardiosis vary with the different *Nocardia* species. Accurate identification of the species is crucial to make the diagnosis.

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Introduction

Members of the genus *Nocardia* are associated with the group of microorganisms known as the aerobic actinomycetes and belong specifically to the family Mycobacteriaceae. *Nocardia* are ubiquitous in the environment and can be found worldwide as saprophytic components in fresh and salt water, soil, dust, decaying vegetation, and decaying faecal deposits from animals [1]. They are Gram-positive and weakly acid-fast, branching bacteria whose hyphae are often fragmented to coccobacillary forms [2]. *Nocardia* species are facultative intracellular pathogens, and the pathogenesis of nocardiosis is complicated. Although a large number of species have been characterized both phenotypically and genotypically within the genus, the genotype remains greatly heterogeneous and continues to evolve [1]. Several species have been implicated in human infections, but the geographical prevalence of each may vary greatly throughout the world. Some species are more prevalent in geographical locations with a specific climate [1].

Nocardiosis is an uncommon bacterial infection with a wide variety of clinical manifestations in immunocompetent and immunocompromised patients. The number of cases reported in the literature is increasing. This might be due to an absolute increase in the number of immunocompromised patients but also to improvement in laboratory techniques to detect nocardiosis. Host resistance to nocardial infection depends on neutrophils in early lesions and then the cell-mediated immune response [1]. The most common predisposing factors to opportunistic *Nocardia* infections are long-term steroid usage, chronic obstructive pulmonary disease (COPD), neoplastic disease, and human immunodeficiency virus (HIV) infection [3,4]. Clinical manifestations of

nocardiosis range from cutaneous infections caused by traumatic inoculation in normal hosts to severe pulmonary and central nervous system diseases in immunocompromised hosts.

The aim of this study was to assess the species distribution of *Nocardia* isolates based on the molecular methods in a teaching hospital over an 11-year period, and to investigate clinical manifestations, microbiological characteristics, response to treatment, and outcome of nocardiosis.

Materials and Methods

Patients and setting

This study was conducted at National Taiwan University Hospital (NTUH), a 2000-bed tertiary care centre in northern Taiwan. Patients with nocardial infection were identified by the Bacteriology Laboratory of NTUH from January 1998 to June 2008. The clinical charts of all patients included in this study were retrospectively reviewed. Information on age, gender, underlying immunocompromised conditions including history of immunosuppressant drug use, corticosteroid therapy, diabetes mellitus, COPD, chronic liver disease, chronic kidney disease, malignancy, organ transplantation, HIV infection, types of clinical specimen positive for *Nocardia* spp. and outcome were analysed.

Definitions

Disseminated nocardiosis was defined as the isolation of *Nocardia* species from specimens from two or more non-contiguous organs such as lungs, lymph node, skin, brain or blood. A diagnosis of pulmonary nocardiosis required at least one positive culture from respiratory samples, and the presence of clinical symptoms and a new lesion on chest xray film at admission. The respiratory samples included expectorated sputum, endotracheal aspiration, pleural effusion, bronchoalveolar lavage or lung tissue obtained from biopsy. Long-term steroid usage was defined as prescription of oral prednisolone at least 10 mg/day for > 2 months before the infection episode. Patients who had any one of bronchiectasis, COPD or pneumoconiosis with previous symptoms and compatible old lesions on chest xray films were categorized as having underlying chronic lung disease. Mortality was defined as death from all causes during the study episode of hospitalization.

Bacterial isolates

Identification of *Nocardia* species was based on positive Gram stain (Gram-positive branching, beaded, and filamentous bacilli) and positive modified acid-fast stain results, colonial morphotypes, and conventional biochemical reactions, including hydrolysis of casein, xanthine, hypoxanthine and tyrosine. All isolates of identified and unidentified *Nocardia* species, based on these conventional methods, were further identified or confirmed by 16S rRNA gene analysis [5]. Partial sequencing analysis of the 16SrRNA gene of the isolates was performed using primers Noc1 (5′-GCTTAACACATGCAAGTCG-3′) (positions 46–64, *Escherichia coli* numbering system) and Noc2 (5′-GAATTCCAGTCTCCCCTG-3′) (positions 663–680, *E. coli* numbering system) [5]. The sequences were compared with published sequences in the 16SrRNA database. The closest matches and GenBank accession number were obtained. For the isolates causing disseminated nocardiosis and unusual *Nocardia* species, susceptibility testing of the agents used in the patients with these infections was used. The agar dilution method was used for susceptibility testing, in accordance with the guidelines recommended by the NCCLS [6].

Results

Microbiological investigation

A total of 164 *Nocardia* isolates were identified from 134 patients during the 11 years. After reviewing the medical records of these patients, 113 patients were confirmed as having *Nocardial* infection. Of 113 episodes of nocardiosis, *N. brasiliensis* (n = 54) was the most common pathogen, followed by *N. asteroides* (n = 36), *N. farcinica* (n = 7), *N. flavorosea* (n = 4), *N. otitidiscaviarum* (n = 3), *N. nova* (n = 3), *N. beijingensis* (n = 2) and one each of *N. puris*, *N. jinanensis* and *N. takedensis*. One isolate was not available for further identification to species level (Table 1). Most of the pulmonary infections were caused by *N. asteroides,* but *N. brasiliensis* caused most of the cutaneous infections. Among patients with disseminated nocardiosis, *N. asteroides* was the most common pathogen, followed by *N. farcinica.*

Clinical features

The demographical and clinical data of patients and the annual numbers of nocardiosis cases are summarized in Table 1 and Fig. 1, respectively. Primary cutaneous *Nocardia* infection was the most common presentation in 64 (56.6%) patients. *Nocardia* caused pulmonary infection in 38 (33.6%) patients, disseminated infection in eight (7.1%) brain abscess in two (1.8%) patients and one patient with acute mastoiditis. The clinical characteristics of the eight patients with disseminated nocardiosis are summarized in Table 2.

All of these patients had pulmonary involvement and five of them had brain abscesses. The MICs of trimetho-

TABLE 1. Clinical manifestations, microbiological characteristics and outcomes of 113 patients with nocardiosis

Variables	No. (%) of all patients (*n* = 113)	No. (%) of patients with pulmonary infection (*n* = 38)	No. (%) of patients with cutaneous infection (*n* = 64)	No. (%) of patients with disseminated infection (*n* = 8)
Age, years (mean ± SD)	55.8 ± 19.1	57.5 ± 17.2	54.5 ± 20.7	59.0 ± 17.3
Male:female	79:34	29:9	41:23	6:2
Underlying disease condition				
Diabetes mellitus	17 (15.0)	6 (15.8)	8 (12.5)	1 (14.3)
Chronic kidney disease	16 (14.2)	5 (13.2)	6 (9.4)	4 (57.1)
Autoimmune disease	16 (14.2)	7 (18.4)	3 (4.7)	2 (28.6)
Solid cancer	12 (10.6)	4 (10.5)	4 (6.3)	3 (42.9)
Chronic lung disease	11 (9.7)	10 (26.3)	0 (0.0)	1 (14.3)
Chronic liver disease	10 (8.8)	2 (5.3)	6 (9.4)	0 (0.0)
Transplant recipient	10 (8.8)	4 (10.5)	3 (4.7)	2 (28.6)
Haematological cancer	7 (6.2)	3 (7.9)	3 (4.7)	0 (0.0)
Thyroid dysfunction	5 (4.4)	1 (2.6)	4 (6.3)	0 (0.0)
AIDS	3 (2.7)	1 (2.6)	2 (3.1)	0 (0.0)
Receiving immunosuppressant	14 (12.4)	5 (13.2)	5 (7.8)	2 (28.6)
Receiving steroid	23 (20.4)	11 (28.9)	6 (9.4)	2 (28.6)
Mortality	8/100 (8.0)	5/36 (13.9)	1/52 (1.9)	2/8 (25.0)
Nocardia spp.				
N. brasiliensis	54 (47.8)	2 (5.3)	52 (81.3)	0 (0.0)
N. asteroides	36 (31.8)	22 (57.9)	7 (10.9)	5 (62.5)
N. farcinica	7 (6.3)	3 (7.9)	0 (0.0)	3 (37.5)
N. flavorosea	4 (3.5)	3 (7.9)	1 (1.6)	0 (0.0)
N. otitidiscaviarum	3 (2.7)	2 (5.3)	1 (1.6)	0 (0.0)
N. nova	3 (2.7)	3 (7.9)	0 (0.0)	0 (0.0)
N. beijingensis	2 (1.8)	2 (5.3)	0 (0.0)	0 (0.0)
N. puris	1 (0.9)	1 (2.6)	0 (0.0)	0 (0.0)
N. jinanensis	1 (0.9)	0 (0.0)	1 (1.6)	0 (0.0)
N. takedensis	1 (0.9)	0 (0.0)	1 (1.6)	0 (0.0)
Nocardia sp.*	1 (0.9)	0 (0.0)	1 (1.6)	0 (0.0)

*The isolate was not available for further identification to species level.

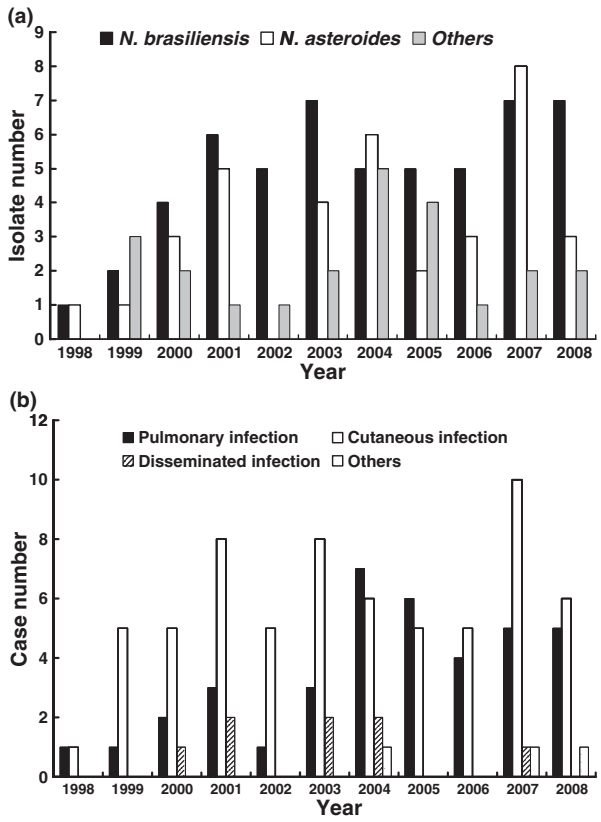

FIG. 1. The annual number of nocardiosis cases from January 1998 to June 2008 according to species of *Nocardia* (a) and types of infections (b).

prim/sulfamethoxazole against seven isolates varied, ranging from 2 to 64 μg/dL, whereas amikacin had the lowest MICs of 0.25 and 1 μg/mL against two isolates. Seven of the eight patients received sulfonamide-based therapy and two patients died during the episode of disseminated nocardial infection.

The clinical and microbiological features of 15 cases of nocardiosis caused by the unusual *Nocardia* species, including *N. otitidiscaviarum*, *N. jinanensis*, *N. flavorosea*, *N. takedensis*, *N. nova*, *N. beijingensis* and *N. puris* are summarized in Table 3. All of the 15 pathogens from these cases were identified by conventional methods and by 16S rRNA gene analysis. *Nocardia flavorosea* caused pulmonary infection in three immunocompromised patients and cellulitis in one immunocompetent patient with tattoo wound. *Nocardia nova* caused pneumonia in two heart transplant recipients and empyema thoracis in one patient with autoimmune disease who was receiving steroid therapy. A gardener with a history of exposure to soil had cellulitis caused by *N. jinanensis*. One diabetic patient had *N. takdensis* cellulitis, but she did not recall any recent insect bite, injury or wound and denied any exposure to a soil environment. Only one fatal case of acute respiratory failure was caused by *N. puris*. Trimethoprim/sulfamethoxazole showed good *in vitro* activities against most of these unusual isolates, except *N. otitidiscaviarum* (MICs of 16 mg/L). MIC of *N. puris* isolate to imipenem was 1 mg/L.

TABLE 2. Summary of clinical characteristics and outcome of eight patients with disseminated nocardial infection

No. (year)	Age years/sex	Underlying diseases or condition	Sites of infection	*Nocardia* species	GenBank (accession no.)	Specimens of isolate	Antimicrobial therapy (MIC, μg/mL)	Outcome
1. (2000)	31/F	Renal transplant, SLE, Immunosuppressant, and steroid therapy	Lung, brain	*N. asteroides*		Sputum, brain	SXT (2)	Survived
2. (2001)	72/M	Chronic obstructive pulmonary disease	Lung, brain	*N. asteroides*		Lung aspirate	SXT (8), MIN	Survived
3. (2001)	61/M	Chronic kidney disease, renal transplant, immunosuppressant treatment	Lung, Lymph node	*N. asteroides*		Sputum, neck lymph node	SXT (4)	Survived
4. (2003)	68/F	Diabetes mellitus, chronic kidney disease	Lung, brain	*N. asteroides*		Sputum, lung aspirate	Cefpime + AM (0.25), SXT (4)	Survived
5. (2003)	70/M	Gastric cancer	Lung, brain	*N. asteroides*		Sputum	Cefpime + AM (1), SXT (64)	Survived
6. (2004)	68/M	ESRD, ITP with splenectomy, colon cancer, steroid therapy	Lung, brain	*N. farcinica*	EU417670.1	Sputum, blood	MEP (4) + SXT (4); SXT(4)	Survived
7. (2004)	32/M	Oral cavity cancer	Lung, blood	*N. farcinica*	EU417670.1	Sputum, blood	MEP (4), SXT (4)	Died (1 month after diagnosis)
8. (2007)	70/M	Bronchiectasis, Sjögren's disease, steroid therapy	Lung, blood	*N. farcinica*	EU417670.1	Sputum, blood	TZP	Died (2 days after diagnosis)

AM, amikacin; MEP, meropenem; MIN, minocycline; SXT, trimethoprim-sulfamethoxazole; TZP, piperacillin/tazobactam.

Brain involvement

A total of 28 patients underwent either computed tomography (CT) or brain magnetic resonance imaging (MRI) in this series. Among them, four patients had positive brain image findings with multiple brain abscesses and another three patients had a solitary brain abscess. The temporal lobe was the most common site of involvement, followed by the frontal lobe. Neurological symptoms, including unilateral weakness, vertigo and incoherent speech, presented in only four patients.

Treatment and outcomes

Eighty-eight patients a received sulfonamide-containing antibiotic and 13 received combined medical and surgical treatment. Medical records adequate to determine outcome were available in 100 of 113 patients.

The crude mortality rate was 8.0% (8/100), and was lowest for primary cutaneous infection (1.9%) and highest for disseminated disease (25.0%).

Discussion

Nocardia are slow-growing organisms that are found extensively worldwide, and the genus *Nocardia* is rapidly expanding, with at least 80 species described (http://www.bacterio.cict.fr/n/nocardia.html) to date. *Nocardia asteroides* is the most common *Nocardia* species associated with human disease [7,8]; however, some *Nocardia* species are more prevalent in geographical locations with a specific climate. For instance, *N. brasiliensis* is associated with tropical environments and often observed in the southern USA [9–11]. *Nocardia farcinica* has been reported more frequently in western European countries [12,13]. This study of 113 patients was performed in a subtropical area where *N. brasiliensis* is the most common nocardial pathogen, followed by *N. asteroides* and *N. farcinica*. Previous studies [1,14–16] showed that pulmonary nocardiosis is the most common nocardial disease, especially in immunocompromised hosts. However, during the 11-year period of this survey, we found that primary cutaneous nocardiosis was the most common presentation of all *Nocardia* infections, followed by pulmonary involvement. These differences among study findings could be entirely due to geographical variations in *Nocardia* spp. distribution. *Nocardia brasiliensis* was the most common pathogen in this study and the majority of primary cutaneous nocardiosis cases were caused by *N. brasiliensis*.

Identification of clinical isolates beyond the genus level is important since *Nocardia* species differ in the clinical spectrum of the disease they cause and their susceptibility to antibiotics [17]. After presumptive identification, final determination is now accomplished in reference labs using molecular techniques, such as 16S rRNA sequence analysis. This study reports the first isolates of *N. flavorosea*, *N. nova*, *N. puris*, *N. beijingensis*, *N. jinanesis* and *N. takedensis* from Taiwan, and these rare strains caused pulmonary and cutaneous infections in 15 patients.

Nocardia flavorosea was originally isolated from soil by Chun *et al.* in 1998 [18]. To the best of our knowledge, this is the first reported case series of human infection with *N. flavorosea*. It caused nocardiosis in three immunocompromised patients with pulmonary infection and another immunocompetent woman with tattoo wound infection. Though optimal therapy for *N. flavorosea* infection has not been

TABLE 3. Summary of clinical characteristics and outcomes of 15 patients with nocardiosis caused by unusual *Nocardia* species

No. of patient (year)	Age (years)/ sex	Underlying diseases or condition	*Nocardia* species	GenBank (accession no.)	Clinical diagnosis	Site of isolate	Antimicrobial therapy (MIC, μg/mL)	Outcome
1. (1999)	73/M	Nil	*N. jinanensis*	DQ462650.1	Cellulitis	Skin pus	SXT (4)	Improved
2. (1999)	29/M	AIDS	*N. flavorosea*	EU841599.1	Pneumonia	Sputum	SXT (4)	Improved
3. (1999)	68/F	Chronic kidney disease, diabetes mellitus	*N. takedensis*	AB156277.1	Cellulits	Skin pus	SXT (4)	Improved
4. (2000)	58/M	Heart transplant, immunosuppressant therapy	*N. nova*	DQ840026.1	Pulmonary infection	Lung aspirate	SXT (8)	Improved
5. (2001)	64/M	Heart transplant immunosuppressant therapy	*N. nova*	DQ840026.1	Pulmonary infection	Lung biopsy	SXT	Improved
6. (2002)	66/M	Autoimmune haemolytic anaemia, steroid therapy, chronic hepatitis C, diabetes mellitus	*N. nova*	DQ840026.1	Empyema	Pleural effusion	SXT + CIP + VATS decortication	Improved
7. (2003)	21/M	Immunosuppressant therapy, dermatomyositis	*N. beijingensis*	DQ659901.1	Pneumonia	Sputum	SXT (4)	Improved
8. (2004)	75/F	Bronchiectasis	*N. beijingensis*	DQ659901.1	Pulmonary infection	Sputum	SXT (4)	Improved
9. (2004)	81/M	Idiopathic pulmonary fibrosis, steroid therapy	*N. puris*	AB097455.1	Pulmonary infection	Endotracheal aspirate	Imipenem (1)	Died
10. (2005)	51/M	Nil	*N. otitidiscaviarum*	DQ659912.1	Pulmonary infection	Bronchial washing and sputum	SXT (16)	Improved
11. (2005)	34/F	Tattoo wound	*N. flavorosea*	EU841599.1	Cellulitis	Skin pus	SXT (4)	Improved
12. (2005)	63/M	Steroid therapy, chronic kidney disease	*N. flavorosea*	EU841599.1	Pulmonary infection	Lung aspirate	SXT (4)	Improved
13. (2006)	89/M	Lung cancer, chronic pulmonary obstructive disease	*N. otitidiscaviarum*	DQ659912.1	Pulmonary infection	Bronchial washing and sputum	SXT (16)	Died
14. (2007)	79/M	Nil	*N. otitidiscaviarum*	DQ659912.1	Cutaneous infection	Skin pus	Unknown	Unknown
15. (2008)	84/M	Chronic myelogenous leukaemia, chronic pulmonary obstructive disease, steroid therapy	*N. flavorosea*	EU841599.1	Pulmonary infection	Sputum	SXT (4)	Improved

established, all four patients responded well to sulfonamide treatment. *Nocardia jinanensis,* a novel species, was first isolated from soil samples [19], but its clinical significance was unknown. Here we report the first case of *N. jinanensis* cellulitis in a gardener, who was thought to be infected because of soil contact. In 2003, a new species of *Nocardia, N. puris*, was described and isolated from a human abscess in Germany [20]. Three years later in Japan, the second strain of *N. puris* was isolated from an 81-year-old man with choroiditis [21]. Here, we report the third case of *N. puris,* which was recovered from endotracheal aspirates and caused a fatal pneumonia in a patient receiving steroids. *Nocardia takedensis* was recently isolated from a sediment sample taken from the moat surrounding Takeda Shrine and only one case of human infection, without a detailed clinical description, has been reported, by Watanabe *et al.* [22]. We report the second case of human infection by *N. takedensis,* which was isolated from a biopsy of foot tissue. The portal of entry of the organism in our patient was not easily clarified because of the absence of any recent contact history or environmental conditions suitable for propagation of the organism. We supposed that the organism might have gained access via a contaminated trivial cutaneous lesion. Our results are consistent with previous reports [22,23] that *N. nova* can cause opportunistic infection in transplant recipients and cancer patients, but thoracic empyema due to *N. nova* has never been reported.

Our report suggests that the clinical manifestations of *N. nova* are protean among severely immunocompromised patients. Wang *et al.* [24] first isolated *N. beijingensis* from soil in China in 2001 and Kageyama *et al.* [25] reported this new species in human infectious samples in 2004. Here, we report two cases of pulmonary infection due to *N. beijingensis,* and both patients improved after treatment with trimethoprim/sulfamethoxazole. However, it is believed that some of these unusual *Nocardia* species are widely distributed in South-East Asia, including China and Japan [21]. Therefore, diseases caused by these microorganisms may be underreported. Because of the diversity of *Nocardia* species, accurate identification is imperative before proper treatment can be determined. Studies of more clinical isolates are needed to decipher the spectrum of clinical diseases caused by these rare pathogens.

Disseminated nocardiosis has been rarely reported [14–16,26,27]; eight cases were identified in our study. In most of these cases the patients were immunocompromised and

the infections were caused by *N. asteroides*. All of these cases had pulmonary involvement, which, not surprisingly, accounted for the origin of the dissemination. Although five patients had brain abscesses, three patients did not have a focal neurological or meningeal sign. Although disseminated nocardiosis is supposed to occur via haematogenous spread, only two patients had a blood culture positive for *Nocardia*. All eight patients received trimethoprim/sulfamethoxazole-based therapy, and only two cases with nocardial bacteraemia died, despite the wide range of MICs of trimethoprim/sulfamethoxazole in the *in vitro* study. Further clinical studies are needed to establish the relationship between *in vitro* susceptibility and *in vivo* results. Furthermore, our findings suggest the importance of brain imaging and blood culture for the diagnosis of disseminated nocardiosis, especially in immunocompromised patients.

In this study, isolated brain abscess was found in two patients; one of these infections was caused by *N. farcinica* and the other by *N. asteroides*. Five of the eight patients with disseminated infection had brain involvement. In fact, 28 patients had previously undergone brain CT or MRI when pulmonary nocardial infection was diagnosed. Among them, four patients had neurological symptoms but another three patients with nocardial brain abscess did not have any neurological deficits. These findings suggest that brain imaging should be performed routinely in patients with pulmonary nocardiosis to detect possible brain abscess even in asymptomatic patients.

Acute mastoiditis is an uncommon complication of otitis media and is rarely caused by *Nocardia* spp. [28,29]. Most of the reported cases of acute mastoiditis [28,29] occurred in immunocompromised patients. One patient in this study, a 37-year-old man with nasopharyngeal carcinoma who had received concurrent chemo-radiotherapy, developed *N. asteroids*-related acute mastoiditis. The infection was cured by trimethoprim/sulfamethoxazole monotherapy. Although this clinical entity is extremely rare, it may have a fatal outcome by evolving into a brain abscess [28].

In conclusion, nocardiosis is not rare in Taiwan. It is a protean disease that manifests with different clinical and microbiological features depending on the infecting *Nocardia* species. Therefore, accurate identification of *Nocardia* species using molecular techniques is important to make the diagnosis and to elucidate the epidemiology. Fortunately, our findings indicate that a sulfa-containing regimen remains effective in treating nocardial infection.

Transparency Declaration

All authors declare no conflicts of interest.

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